2003-505255/47 B03 (B02) **SHIO 2001.12.05**
SHIONOGI & CO LTD *WO 2003047564-A1
2001.12.05 2001-371436(+2001JP-371436) *(2003.06.12)* A61K 31/343, 31/4196, 31/44, 31/443, 31/4439, 31/505, 31/506, 31/538, 31/55, 45/00, A61P 31/18, 43/00, C07D 213/50, 239/34, 265/36, 307/83, 401/06, 403/06, 405/06, 413/06

HIV integrase inhibitor comprises new and known cyclic compounds (Jpn)

C2003-135097 N(AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW) R(AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SI SK SL SZ TR TZ UG ZM ZW)

Addnl. Data: MURAI H, KUROSE N
2002.12.02 2002WO-JP12582

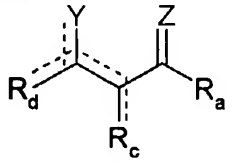
B(6-A1, 6-E2, 7-D6, 14-A2B1, 14-D7) .5

NOVELTY

HIV integrase inhibitor comprises a cyclic compound (I).

DETAILED DESCRIPTION

HIV integrase inhibitors comprise a cyclic compound of formula (I) or its salts or prodrugs.



(I)

$R_c + R_d$ = optionally fused ring;
Y = O, S, NR_e, OR_e, SR_e, NR_eR_f or $N=R_e$;
R_e, R_f = A, or
$R_e + R_d$ = a ring;
Z = O, S or NH;
R_a = $C(=X)R_b$ or nitrogenous heteroaromatic ring attached via C and containing at least one non-substituted N;

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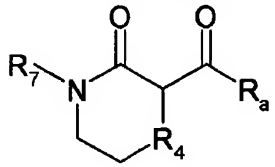
X = O, S or NH;
at least one of $R_c + R_d$, $R_d + R_c$ or R_a = substituted by $Z_1Z_2Z_3R_1$ (optionally substituted by A);
Z_1, Z_3 = a bond or optionally substituted alkylene or alkenylene;
Z_2 = CH(OH), S, SO, SO_2, SO_2NR_2, NR_2SO_2, O, NR_2, NR_2CO, $CONR_2$, COO, OCO, CO or optionally substituted alkylene or alkenylene;
R_2 = H or optionally substituted alkyl, alkenyl, aryl or heteroaryl;
R_1 = optionally substituted aryl, heteroaryl, cycloalkyl, cycloalkenyl or heterocyclyl;
A = H, halo, COOAlk, COOH, Alk_1, $OAlk_1$, Alk_1OAlk_1, NO_2, OH, alkenyl, alkynyl, SO_2Alk, SAlk, nitroso, N_3, amidino, guanidino, CN, NC, SH, SO_2NH_2, $NHSO_2$, CHO, COAlk, OCOAlk, hydrazino, morpholino or optionally substituted amino, cycloalkyl, cycloalkenyl, heterocyclyl, carbamoyl, Ar, AlkAr, OAr, SAr, OAlkAr, AlkOAr, AlkSAr, SO_2Ar or SO_2AlkAr;
Alk_1 = alkyl or haloalkyl;
Ar = aryl or heteroaryl,
provided that the following compounds are excluded: [5-(4-fluorobenzyloxy)-3-oxo-2,3-dihydrobenzofuran-2-yl]-oxoacetic acid or its methyl ester, [4-(4-fluorobenzyloxy)-3-oxo-2,3-dihydrobenzofuran-2-yl]-oxoacetic acid or its methyl ester, [5-(4-fluorobenzyl)-3-oxo-2,3-dihydrobenzofuran-2-yl]-oxoacetic acid or its methyl ester, [5-(4-fluorobenzyl)-2-(pyridine-2-carbonyl)benzofuran-3-one, [5-(4-fluorobenzyl)-2-(pyrimidine-2-carbonyl)benzofuran-3-one, (6-benzyloxy-1-oxo-indan-2-ylidene)hydroxyacetic acid and its ethyl ester and (7-benzyloxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-ylidene)hydroxyacetic acid.

An INDEPENDENT CLAIM is also included for compounds of formula (IA) and their salts and prodrugs.



(IA)

R_4 = a bond, $CHACH_2$ or CH_2CHA, and
R_a = nitrogenous heteroaromatic ring attached via C and containing at least one non-substituted N substituted by $Z_1Z_2Z_3R_1$ and A.

ACTIVITY

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Anti-HIV.

MECHANISM OF ACTION

Integrase-Inhibitor.
In assays, (6,7-dihydro-3H-cyclopentanepyrimidin-7-yl)-(5-phenoxy)pyrimidin-2-yl)methanone had an IC_{50} value for HIV integrase of 0.50 μg/ml.

USE

Used for treating and preventing AIDS.

ADMINISTRATION

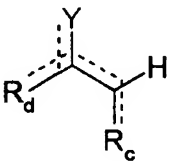
The dosage is 0.05-3000 (preferably 0.1-1000) mg/day orally or 0.01-1000 (preferably 0.05-500) mg/day parenterally. (I) are preferably administered with reverse transcription and reductase inhibitor.

EXAMPLE

No suitable example is given.

TECHNOLOGY FOCUS

Organic Chemistry - Preparation: Preparation of (I) comprises e.g. reacting a cyclic compound of formula (II) with $LC(=Z)R_a$ (III) in the presence of a base.



(II)

L = a leaving group.
(119pp2533DwgNo.0/0)

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